Comments on the "genotype first diagnosis" controversy

To the Editor:

I read with great interest the two letters about the pros and cons of the "Genotype First Diagnosis" announced in the front page of the May 2009 issue of *Genetics in Medicine*.[1,2] I cannot agree more with Drs. Saul and Moeschler.[1] Although the new technologies, mainly microarray-based comparative genomic hybridization, have significantly increased the number of patients for whom we establish a diagnosis,[2] there is no question that a good clinical evaluation is still of utmost importance.

The promotion of "testing first" is attractive to many primary care physicians (general pediatricians and some subspecialists) who hope that an abnormal result will provide the diagnosis. The testing first is an example of the "sampling the universe" diagnostic approach described by the late Frank A. Oski.[3] This approach is commonly practiced by young physicians. Instead of the use of "hypothesis generation" as the diagnostic method recommended by Oski, and used by most clinical geneticists, a growing number of physicians rely on testing for their diagnoses.

I believe this policy of testing first should not be endorsed by the American College of Medical Genetics (ACMG). It is not an appropriate medical practice, because it increases the cost of medicine, and there are many results that will still need the interpretation of the geneticist and genetic counselor and the evaluation of the family. The attempt to end the "family's diagnostic odyssey" through indiscriminate testing no doubt has a high cost. The number of cases where microarray has been requested by the referring physician before a genetics evaluation is increasing. Furthermore, a significant number of such patients are referred with normal microarray results. By comparison, when a patient has undergone a comprehensive evaluation, including a detailed history and physical examination, microarray seems to yield a higher rate of abnormalities (Lacassie Y, Myrtle V, Sathyamoorthi S, unpublished study).

There is no doubt that our primary goal as physicians is to serve our patients' best interests. In that pursuit, an accurate diagnosis is the cornerstone. In a testing-first approach to genetics, we deemphasize the importance of the family evaluation and phenotype. We may perform unnecessary testing with a consequent high expense. When the diagnostic approach combines clinical skills with the appropriate medical test, the sensitivity of the test is certain to increase. In the case of microarray, it seems clear that the appropriateness of testing is best gauged by a clinical geneticist.

There is also no doubt that that there is a "critical shortage" of medical geneticists, as noted by Dr. Ledbetter. More specifically, however, the shortage may reflect the declining number of clinical geneticists. Such a trend will undoubtedly continue so long as molecular testing advances in its diagnostic ability. However, I would like to point out that the major reason why I am commenting on this controversy is the lack of challenge for the clinical geneticist. The evaluation of patients with an unknown diagnosis is challenging, constitutes clinical research, and is intellectually gratifying when your diagnostic hypothesis is confirmed through a specific test. This is why many geneticists enjoy their job. Otherwise dealing with patients with multiple congenital anomalies, mental retardation, or other developmental issues, for which there are few treatments to offer, other than counseling, is not compelling at all to most physicians and medical students.

I openly admit to the referring physicians that I prefer to evaluate the patient without a diagnosis and before any testing. What makes our specialty interesting is the challenge to try to establish an etiological diagnosis.[4,5] Most geneticist will agree that it is quite disappointing when the patient is referred for evaluation and counseling after the diagnosis was already established. Certainly, the ACMG should be the center of discussion for this topic. Before reading these two letters,[1,2] I proposed some aspects of this subject to discuss at the next meeting of the ACMG in New Mexico.

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Reply to letter from Drs. Ledbetter, Saul, and Moeschler

I would like to respond to the letters from Drs. Ledbetter, Saul, and Moeschler. To argue the preferability of a "genotype first" versus "phenotype first" approach is akin to arguing over the placement of the deck chairs on the Titanic. In the face of personalized medicine, direct to consumer marketing, and the skyrocketing number of genetic tests, there are far greater issues that need to be recognized and new approaches that need to be created. The community of clinical genetics can choose to be a part of the genetically based revolution in health care that they helped to create or they can let new implementation models pass them by while quibbling over whether a "genotype first" or "phenotype first" approach is best.

In an ideal world, a skilled physician, such as a clinical geneticist, would be at the helm of the diagnostic workup of a child with developmental delays. Insight based on the findings of a complete physical examination and family history would guide appropriate testing, allowing appropriate and accurate genetic counseling. However, given the realities of today's health care system, it is critical to ask ourselves whether achieving this ideal is realistic.

Consider the viewpoint of a busy primary care physician, challenged with shepherding a family through what may be the beginning stages of the diagnostic odyssey. Chances are that the family has no (or inadequate) health insurance. The mother likely will be challenged by taking more than a few days off from work for other appointments, and the physician envisions multiple subspecialty referrals in addition to occupational therapist, physiotherapist, and other services in this family's future. The pediatric subspecialists may well be in another city and have a waitlist of several months. The physician must consider all of these factors when making referrals and recommendations. The physician must also consider how to help the family get the most out of these referrals. If the physician orders the

first line of diagnostic tests (including microarray) at the time of referral, it is possible the diagnosis will be established months earlier than if the test had to be ordered by the specialist. Alternatively, if the test is negative, it has eliminated several conditions from the differential diagnostic. In either situation, the specialist will have more information at the time of the appointment, potentially shortening the diagnostic odyssey and possibly enabling the family to access services, such as early intervention and treatment protocols, in a more timely fashion.

Consider this analogy. A conductor of a major orchestra believes that the best way to hear great music is in a concert hall. In his opinion, a recording is a poor substitute and should not be tolerated. Obviously, this is simply not realistic. Recordings are the only way that a certain segment of the population will ever hear such music, and although it may not be of the same high quality as listening in the concert hall, it is certainly better than no music at all. One cannot let perfect be the enemy of good.

In a way, however, the entire discussion to this point is of limited relevance. The fact of the matter is that primary care physicians will be ordering genetic tests, sometimes appropriately and sometimes not. With the advent of direct to consumer companies, the public will also be ordering genetic tests. The genetics community has spent considerable time pointing out all the potential negative consequences of these testing scenarios. When rearranging deck chairs, the community has neither examined the potential opportunities of the paradigm shift nor crafted a cohesive response.

The genetics community is now suffering from a self-inflicted identity crisis because of its own success: the identification of the genetic causes of disease. This exchange of letters indicates that this is the time for reassessment, reorganizing, and redefining the profession.

Traditionally, the majority of patients in a genetics clinic are in search of a unifying diagnosis. However, I predict that the genetics clinic of the future will look very different. The "in search of diagnosis" patients will become a smaller proportion as other indications become more common. The new "typical" patients will be as follows:

- Healthy adults asking, "What am I at risk for based on my family history? Based on the results of my genome scan? What should I be doing based on these risks?"
- My child has this test result indicating a complex condition Z. Our family doctor says that you are best able to manage it.
- I have genetic condition Y, which was diagnosed when I was a child. Is there anything new I need to know about?

These new patients with new questions provide new opportunities for the genetics community, but only if we recognize this as an opportunity rather than an infringement on our territory. We must welcome these developments and aid in their implementation. How can we do this? I can make some suggestions. I am sure there are numerous others if the clinical genetics community would come together to embrace the possibilities. Potential suggestions are as follows:

1. Lobby to get electronic pedigree drawing tools embedded into electronic medical records. This will enable the primary care physician (or the patient himself) to complete the family history before the genetics appointment. Not only does this save time in the genetics appointment but also ensures that only those families appropriate for counseling would be referred to the geneticist by the primary care physician, who would have already reviewed the pedigree. Enabling any health care provider to easily view a pedigree as a routine part of a medical record will enable and increase its use.
2. Educate the geriatricians and adult medicine community about the need for genetic testing. Because testing for late-onset diseases becomes available, it will be critical to test the clinically diagnosed affected individuals first to provide informative results to the rest of the family for possible future testing for them.
3. Create a web-based "queryable" database of information that directly addresses the variety of results from direct to consumer genetic testing companies. This database could detail which results are actionable and which not. For example, a test that shows that a particular disease risk was doubled at first sounds as if it has clinical utility. However, explaining that the risk for that condition is now two in a million instead of one in a million provides context and clarity. Most importantly, this approach could help to ensure that those individuals who have a result that requires follow-up seek out the genetics provider. By adding the zip code in this database, they could get the closest genetics providers.
4. Get out of the "diagnose and adios" mode of thinking. There are patients with complex genetic conditions that affect multiple body systems. These individuals often see a bevy of subspecialists without a genetically knowledgeable continuity provider. Geneticist could play a unique role by being the maestro of this orchestra. Also, by moving into more of a "coordinator" role, geneticists will be able to provide longitudinal care to affected patients by providing continuing counseling to children as they transition into adulthood. It will also allow geneticists to keep families apprised of the latest developments in research and treatments; a field that is poised to grow exponentially.

I realize that these activities may not generate the adrenaline rush of making a diagnosis missed by others. Nevertheless, there are still important contributions to be made using these new models. Reluctance to adapt to and embrace new developments in the medical landscape can lead to obsolescence. Let's get on with making the most of these new opportunities for the benefit of patients and geneticists.

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